

The Analgesic Efficacy of Intradiscal Injection of Bone Marrow Aspirate Concentrate and Culture-Expanded Bone Marrow Mesenchymal Stromal Cells in Discogenic Pain: A Systematic Review

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Abstract: Pain originating from the intervertebral disc (discogenic pain) is a prevalent manifestation of low back pain and is often challenging to treat. Of recent interest, regenerative medicine options with injectable biologics have been trialed in discogenic pain and a wide variety of other painful musculoskeletal conditions. In particular, the role of bone marrow aspirate concentrate (BMAC) and culture-expanded bone marrow derived mesenchymal stromal cells (BM-MSCs) in treating discogenic pain remains unclear. The primary objective of this systematic review was to appraise the evidence of intradiscal injection with BMAC and culture-expanded BM-MSCs in alleviating pain intensity from discogenic pain. Secondary outcomes included changes in physical function after intradiscal injection, correlation between stromal cell count and pain intensity, and anatomical changes of the disc assessed by radiographic imaging after intradiscal injection. Overall, 16 studies consisting of 607 participants were included in qualitative synthesis without pooling. Our synthesis revealed that generally intradiscal autologous or allogeneic BMAC and culture-expanded BM-MSCs improved discogenic pain compared to baseline. Intradiscal injection was also associated with improvements in physical functioning and positive anatomical changes on spine magnetic resonance imaging (improved disc height, disc water content, Pfirrmann grading) although anatomical findings were inconsistent across studies. However, the overall GRADEscore for this study was very low due to heterogeneity and poor generalizability. There were no serious adverse events reported post intradiscal injection except for a case of discitis.

Keywords: BMAC, discogenic pain, bone marrow mesenchymal stromal cells

Introduction

Low back pain (LBP) is a major cause of worldwide disability, with an estimated point prevalence of 30–50% and a lifetime prevalence as high as 80–85%.^{1–3} A common etiology of back pain is discogenic pain, seen in 22–42% of LBP cases.^{4–6} The intravertebral discs (IVDs) are fibrocartilaginous joint-like structures that connect and cushion the vertebrae in the axial skeleton, providing stability while permitting motion between vertebrae.⁷ Aging, genetic factors, and environmental changes have been hypothesized to reduce IVD cell number and alter their metabolism.⁸ With increasing catabolic activity and decreasing anabolic activity, there are changes in the expression and structure of collagens and proteoglycans in the extracellular matrix resulting in decreased IVD strength and internal disc disruption (IDD). Also, IVD is generally avascular which contributes to poor healing.⁹ This above process restricts the regenerative potential of the IVD and limits its ability to uniformly distribute forces causing discogenic pain.¹⁰ Associated changes in the surrounding vertebral body and endplate can also contribute to painful stimuli.¹¹

The treatment of discogenic pain is challenging with the most common modalities being conservative or symptom focused. Conservative measures include oral analgesics, physical therapy, and epidural corticosteroid injections. More invasive treatment options include spine surgery, such as discectomy, spinal fusion, and disc replacement.¹² Recently, there has been significant research devoted to injectable biological treatment options with the potential to not only improve pain, but also decelerate or restore the structure of the IVD, which may potentially alleviate discogenic pain.

There are a variety of biologics that have been studied for treatment of musculoskeletal conditions, most commonly osteoarthritis or tendinopathy, including platelet rich plasma (PRP) and mesenchymal stromal cells (MSCs) derived from adipose tissue, umbilical cord, peripheral blood, and bone marrow.^{13,14} MSCs are a population of multipotent cells that can differentiate along the chondrogenic, osteogenic, and adipogenic lineages *in vitro*.¹⁵ Historically, MSCs have been harvested and isolated from bone marrow, known as bone marrow derived MSCs (BM-MSC), commonly by accessing and aspirating from the iliac crest. This bone marrow aspirate primarily contains hematopoietic cells, adipose tissue, and supportive stromal cells with a small amount of BM-MSCs.¹⁶ The bone marrow aspirate can be used as an injectate without modification, cultured for cell expansion, or minimally modified and concentrated into bone marrow aspirate concentrate (BMAC) through centrifugation.¹⁷ This review will focus on BMAC and BM-MSCs since they are one of the most common biologics used to treat musculoskeletal pain.

The role of BMAC and culture-expanded BM-MSCs in the treatment of discogenic pain from IDD remains unclear. Several non-systematic narrative reviews have been published providing a summary of findings of all biologic agents in the treatment of IDD, although conclusions, quality of evidence, and risk of bias cannot be determined from these broad narrative reviews.^{18,19} The aim of this systematic review is to appraise the evidence on improvement of pain intensity after intradiscal injection of BMAC and culture-expanded BM-MSCs for treatment of discogenic pain.

Methods

Literature Search Strategy

The study protocol was registered under the PROSPERO International prospective register of systematic reviews (CRD42021282340). A literature search was conducted with the assistance of a medical librarian (L.H.). Embase, PubMed/Ovid MEDLINE, EBM Reviews – Cochrane Central Register of Controlled Trials (CENTRAL), and EBM Reviews – Cochrane Database of Systematic Reviews databases were used to conduct the literature review. Publication date range included the entirety of each database and was completed on October 6th, 2021. Controlled vocabulary supplemented with keywords was used to search for studies describing autologous or allogeneic BMAC or BM-MSCs for discogenic back pain. The actual strategy listing all search terms used and how they were combined is available in the [Appendix](#). In addition, a manual search in PubMed and Google Scholar using the terms “bone marrow aspirate concentrate injection for discogenic pain”, “intervertebral disc injection”, and “stromal cell injection for discogenic pain” was conducted to ensure completeness of the review content.

Study Selection

A total of 764 articles were screened in parallel by 2 independent reviewers (Y.F.H., G.M.A.) (Figure 1). Disagreements were resolved by a third independent reviewer (R.S.D.). Out of 764 articles, 756 studies were identified through database searches and eight studies were identified through a manual search. Inclusion criteria included all human studies in the English language that reported pain intensity after intradiscal injection with BMAC or culture-expanded BM-MSCs to treat discogenic pain. Discogenic pain was defined as predominantly low back pain felt to be originating from degeneration or damage to the intervertebral discs. We did not mandate that studies utilize provocative discography for diagnosis of discogenic pain. Studies were included if they described low back pain attributable to degenerative disc disease (e.g. painful annular fissure) that correlated with physical exam findings, or if they described a concordant response with low-pressure provocative discography. Exclusion criteria comprised the following: review articles, animal studies, and conference proceedings.

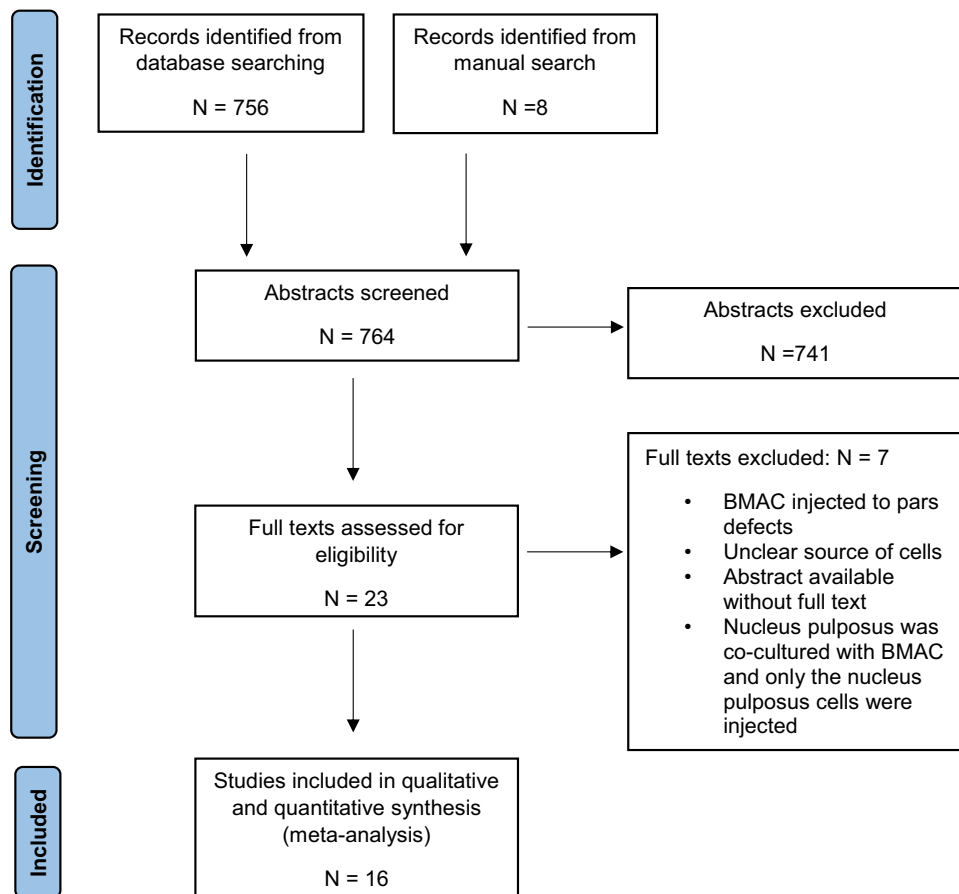


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the literature search and selection process. BMAC, bone marrow aspirate concentrate.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.³⁶

Data Extraction and Outcomes of Interest

The following data were extracted: (1) Study year, (2) Study design, (3) Study funding, (4) Country where the study was performed, (5) Cell/BMAC/BM-MSC source, number of cells and volume of injectate if available, (6) Number of subjects in each arm, (7) Provocative discography inclusion, (8) Age of cohort, and (9) Summary of study findings. The primary outcome of interest was change in pain intensity after intradiscal injection with BMAC or culture-expanded BM-MSCs. Secondary outcomes included correlation of pain intensity based on number or concentration of cells in the intradiscal injectate, change in physical functioning, and change in Magnetic Resonance Imaging (MRI) findings after intradiscal injections with BMAC or culture-expanded BM-MSCs.

Assessment of Risk of Bias

The risk of bias for the studies included was independently evaluated by two reviewers (Y.F.H., E.K.) using guidelines from the Cochrane Collaboration. Risk of bias was assessed in reference to a hypothetical randomized controlled trial (RCT) that randomly selected participants to either receive intradiscal injection of BMAC or culture-expanded BM-MSCs or placebo injection. In reference to this target trial, biases were assessed in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias due to missing data, reporting bias, and other biases. Each domain category was assigned a grade of low risk, high risk, or unclear risk.

If a randomized design was not used, risk of bias was assessed for observational studies based on a hypothetical prospective cohort study that matched participants receiving BMAC or culture-expanded BM-MSCs and would compare the two groups. We used Newcastle-Ottawa quality assessment scale for observational studies that would assess bias based on Selection (Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration of outcome of interest does not present at start), comparability (Comparability of cohorts on the basis of the design or analysis) and Outcome (assessment of outcome, was follow-up long enough for outcomes to occur, adequacy of follow-up of cohorts). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Assessment of Quality of Evidence

The GRADEpro software (Evidence Prime, Inc; <http://grade.pro.org>) was used for GRADE (Grading of Recommendations, Assessment, Development and Evaluations) quality of evidence assessment for each outcome. RCTs are categorized as high-level evidence. This can be downgraded based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. This systematic review contains both RCTs and observational studies. “Observational study” design was chosen as the starting point with the level of evidence categorized as low-level evidence.

Results

Characteristics of Included Studies

Sixteen studies were included in final qualitative analysis without pooling (Figure 1). There were three RCTs,^{20–22} nine prospective cohort studies,^{23–31} three case series,^{32–34} and one retrospective study³⁵ comprising a total of 607 participants. Fifteen studies selected 425 participants with chronic lumbar discogenic pain.^{20–24,26–35} One study selected 182 participants with chronic cervical discogenic pain.²⁵ The age range of the participants were 18–80 years with the majority of the participants between 35 and 55 years. The follow-up time range was 12–72 months. Extracted variables from each study are reported in Table 1.³⁶

Bone Marrow Aspirate Preparation

Thirteen studies used autologous bone marrow aspirate that were either non-concentrated,³⁴ concentrated,^{23,25–31,35} or further processed to obtain culture-expanded BM-MSCs^{24,32,33} for intradiscal injection. Studies^{23,25–31,35} that used BMAC obtained it from the iliac crest and injected 0.5–6 mL of BMAC per disc with concentrations up to 129.6 million of total nucleated cells (TNC)/mL.^{23,25–31,35} One study³⁴ used non-concentrated bone marrow aspirate from the iliac crest and injected 1 mL per disc. Six studies^{20–22,24,32,33} used culture-expanded BM-MSCs and injected 1.73×10^6 to 4.5×10^7 cells per disc in one visit.

Three studies used allogeneic culture-expanded BM-MSCs for intradiscal injection.^{20–22} Amirdelfan et al used bone marrow aspirate, culture-expanded and immunoselected mesenchymal precursor cells from a single healthy donor.²⁰ The participants were injected with either 6×10^6 or 25×10^6 culture-expanded BM-MSCs per disc. Noriega et al used bone marrow aspirate cells from five healthy donors.^{21,22} The participants were injected with 25×10^6 culture-expanded BM-MSCs per disc.

Provocative Discography

Four studies performed provocative discography to confirm discogenic pain as part of the inclusion criteria.^{23,24,34,35} Six studies performed provocative discography on some of their participants.^{20,26,28–30,33} Five studies did not perform provocative discography.^{21,22,27,31,32} One study did not report whether provocative discography was performed.²⁵ The Dallas Scale Grade for the flow of contrast was not reported.

Outcome Measure Tools

Fourteen studies used an 11-point visual analog scale (VAS) to assess pain intensity.^{20–31,33,34} Two studies used an 11-point numeric pain scale (NPS)^{32,35} and one study used the brief pain inventory (BPI).²³ Other secondary outcomes assessed by questionnaires included physical functioning assessed by Oswestry disability index (ODI) in nine studies,^{20–22,24,26,28–30,35} patient

Table 1 Summary of Findings from Included Studies on Use of BMAC and BM-MSc for Intradiscal Disease

Study/Year	Country	Study Design	Study Funding	Source (Cell Count), Volume Injected	Provocative Discography	# of Participants in Each Arm	Age (Mean or Median)	Summary of Study Finding
Amirdelfan et al 2021. ²⁰	USA, Australia	Multicenter RCT	Industry-sponsored	Allogeneic expanded STRO-3+ mesenchymal precursor cells (MPCs) from iliac crest, 2cc per injection	Mixed, (investigator discretion)	100 participants with CLBP were divided into 3:3:2:2 ratio of 18 million MPCs + HA (n=30), 6 million MPCs + HA (n=30), HA control (n=20), or Saline control (n=20)	Mean: 18 million MPC +HA (37.9), 6 million MPC+HA (45.1), Saline (44.5), HA control (40.3)	6 and 18 million MPC-treated groups showed significant improvement in VAS compared to saline (12, 24, 36 M) and HA controls (3, 6M for 6 mil., 3M in 18 mil. group). The 18 million MPC-treated group showed significant improvement in ODI compared to saline controls at 36 months. 18 million MPC group reported improvement in the physical component score (SF-36) compared to controls. There were no significant radiographic improvements in any of the groups.
El-Kadiry et al 2021. ²³	Canada	Prospective study	Industry-sponsored	Autologous BMAC from PSIS (mononuclear fraction containing MSCs CD45-CD44+CD90 +CD105+ selected by Chondrostem, 1-6 cc injected, from PSIS	Yes	13 participants - intradiscal MSC injection 5 participants - posterior spinal chain injections	Median: Intradiscal group 33-78 (63) Posterior spinal chain group 40-77 (57)	At 12M, VAS (MSC 58%vs 13% control) and BPI (-31% vs -2%) scores improved significantly in the intradiscal injected participants compared to the posterior spinal chain injected participants. Opioid use significantly decreased (61.5% MSC group; 20% control) in the intradiscal injected participants. Disc height and spinal canal space size increased in the intradiscal injected participants at 8 and 12M.

(Continued)

Table 1 (Continued).

Study/Year	Country	Study Design	Study Funding	Source (Cell Count), Volume Injected	Provocative Discography	# of Participants in Each Arm	Age (Mean or Median)	Summary of Study Finding
Noriega et al 2017. ²¹	Spain	RCT	Investigator-initiated grant and Industry-sponsored	Allogeneic expanded bone marrow MSC (25x10 ⁶ cells per segment), from 5 donors	No	12 participants – intradiscal MSC injection 12 participants - sham injection in paraspinals	Mean: 38	At 2-, 4-, 6-, and 12M, MSC-injected participants reported improved VAS and ODI. Group of responders (40% of the cohort) in MSC-treated group displayed a quick and significant improvement versus the controls. No significant changes in discs heights and water content between the two groups. Pfirrmann grading favors the MSC-injected group.
Noriega et al 2021. (42M follow-up of Noriega et al 2017) ²²	Spain	RCT	Investigator-initiated grant and Industry-sponsored	Allogeneic expanded bone marrow MSC (25x10 ⁶ cells), from 5 donors	No	12 participants - MSC injection 12 participants - sham injection in paraspinals	Mean: 38	At 42M, VAS and ODI improvement persisted in the MSC-injected group. The decreased Pfirrmann grading was maintained in the MSC-injected participants.
Orozco et al 2011. ²⁴	Spain	Prospective study	Investigator-initiated grant	Autologous expanded bone marrow MSC	Discography part of inclusion criteria (to determine if fibrous ring can hold cells)	Single arm - 10 participants with CLBP received MSC injection	Mean: 35	At 12M, VAS and ODI significantly improved. Disc height did not change, but water content was significantly elevated.

Centeno et al 2017. ³²	USA	Case series (registry-based study)	Industry-sponsored	Autologous expanded in hypoxic cultured bone marrow MSC from PSIS (range 1.73×10^6 to 4.5×10^7) injected with PL; + PL epidural injection before and after MSCs injection	No	33 participants with CLBP received MSCs +PL; epidural injection of PL given before and after MSCs injection Injection at 1 level (n = 8), 2 levels (n = 16), or 3 levels (n = 9)	Mean: 40.3 (range 19–72)	At 36M, the average modified SANE rating improved by 60%. At 3–72M, NPS significantly improved from baseline scores. FRI significantly improved post treatment. 17/20 participants that underwent post-treatment MRI displayed a decrease in posterior disc bulge with average reduction size of 23%. No SAEs.
Pettine et al 2015. ²⁹	USA	Prospective 2-arm study, non-randomized	Not reported bone marrow concentrating devices donated from Celling Biosciences	Autologous BMAC from iliac crest, 2–3cc	Mixed (7 out of 26 participants only (4 in 1 level group, 3 in 2 level group))	26 participants with CLBP received injection. Injection at 1 level (n=13) Injection at 2 levels (n=13)	Mean: 40, (range 18–61) Age < 40 (n =14) Age > 40 (n=12)	At 12M, average VAS and ODI were significantly reduced in all participants with the participants > 40 y.o. and cells < 2K CFU-F/mL experiencing the least improvement. 8/20 participants improved by one modified Pfirrmann grade. Participants > 40 y.o. with < 2K CFU-F/mL demonstrated an overall regression on average of 0.17 per disc. 24/26 participants avoided surgery.
Pettine et al 2016. (24M follow-up of Pettine et al 2015) ²⁸	USA	Prospective 2-arm study, non-randomized	Not reported; bone marrow concentrating devices donated from Celling Biosciences	Autologous BMAC from iliac crest, 2–3cc, avg TNC content 121×10^6 /mL	Mixed (7 out of 26 participants only (4 in 1 level group, 3 in 2 level group))	26 participants with CLBP received injection. Injection at 1 level (n=13) Injection at 2 levels (n=13)	Mean: 40 (range 18–61) Age < 40 (n =14) Age > 40 (n=12)	At 24M, improvement in VAS and ODI scores were sustained. 21/26 participants avoided surgery. 24/26 avoided surgery through 12M. 4/5 participants who opted for surgery had an MSC concentration range of < 2K CFU-F/mL. At 12M, 8/20 participants had at least one Pfirrmann grade improvement on the MRI. None of the discs had worsened.

(Continued)

Table 1 (Continued).

Study/Year	Country	Study Design	Study Funding	Source (Cell Count), Volume Injected	Provocative Discography	# of Participants in Each Arm	Age (Mean or Median)	Summary of Study Finding
Pettine et al 2017. (36M follow-up of Pettine et al 2015) ³⁰	USA	Prospective study, non-randomized	Not reported; bone marrow concentrating devices donated from Celling Biosciences	Autologous BMAC from iliac crest, (2–3mL)	Mixed (7 out of 26 participants only (4 in 1 level group, 3 in 2 level group))	26 participants with CLBP received injection. Injection at 1 level (n=13) Injection at 2 levels (n=13)	Mean: 40, (range 18–61) Age < 40 (n =14) Age > 40 (n=12)	At 36M, improvement in VAS and ODI scores were sustained. 20/26 participants avoided surgery. Participants with > 2K CFU-F/mL tended to have better VAS and ODI scores than those with < 2K CFU-F/mL.
Pettine et al 2018. (5-year follow-up of Pettine et al 2015) ²⁶	USA	Prospective study, non-randomized	Not reported; bone marrow concentrating devices donated from Celling Biosciences	Autologous BMAC from iliac crest, (2–3mL)	Mixed (7 out of 26 participants only (4 in 1 level group, 3 in 2 level group))	26 participants with CLBP received injection. Injection at 1 level (n=13) Injection at 2 levels (n=13)	Mean: 40, (range 18–61) Age < 40 (n =14) Age > 40 (n=12)	No AEs were reported through 5 years of follow-up. 19/26 participants maintained their improved VAS and ODI scores through 60M.
Pettine, K. A. 2017. ²⁵	USA	Prospective study, non-randomized	Not reported	Autologous BMAC from iliac crest, (0.5cc per disc with 0.175cc of 50% glucose and 0.175cc of bicarbonate)	Not reported	182 participants with axial neck pain received intradiscal 1 to 4 level injections Average levels injected 2.44; 1 level (n=33) participants, 2 levels (n=60), 3 levels (n=45), 4 levels (n=44)	Mean: 54.5 (range 18–81)	At 6-, 12-, and 24M, NDI and VAS improved and maintained by an average of 63% and 67%, respectively. There were no AEs.
Pettine et al 2017. ²⁷	USA	Prospective study, non-randomized	Not reported	Autologous BMAC from iliac crest, 2–3cc per disc, maximum 10cc per participant	No	146 participants with CLBP received intradiscal injection (average 3.6 levels)	Mean: 53 (range 17–80)	There were no SAEs. At 3-, 6-, and 12M, participants reported significant improvement in VAS and ODI scores. 2 participants had surgery during the study for indications other than discogenic low back pain.

Elabd et al 2016. ³³	USA	Case series	None reported (conflict of interest – authors are shareholders and employed by BioRestorative Therapies)	Autologous expanded in hypoxic cultured bone marrow MSC from PSIS injected with PL (0.25–1 cc), (15.1–51.6 millions)	Yes – in some participants	5 participants, chronic lumbar radiculopathy	Mean: 40.4 (Range 25–53)	No AEs 4–6 years post-injection. At 4–6 years follow-up, 5/5 participants reported overall improvement (10–90%). 4/5 participants reported improved mobility. There is a linear relationship between the amount of bone marrow MSC injected and overall percent improvement.
Navani et al 2018. ³¹	USA	Prospective study, non-randomized	Not reported	Autologous BMAC 1–2 cc of BMAC or PRP	No	20 participants with CLBP received intradiscal PRP or BMC injection. Not clear which subject received which injectate.	Not reported	No reported AEs. At 6- and 18M, 94% (17/18) and 93% (14/15) of the remaining participants reported >50% in VPS. At 6- and 18M, 100% and 93% of participants reported improvement in SF-36. At 6- and 18M, 89% and 80% of participants reported decreased medication use. Resolution of 1 annular tear on MRI.
Wolff et al 2020. ³⁵		Retrospective analysis	No funding; co-authors are employed by Isto Biologics	Autologous BMAC from PSIS, 2–3cc	Yes	33 participants received intradiscal injection Injection at 1 level (n=8), 2 levels (n=16), 3 levels (n=9)	Mean: 45 (range 32–72)	At 2-, 6–8, 12-, 24-, and 52-weeks, participants reported improvement in the NRS, ODI, and SF-36 scores. However, these improvements were not statistically significant.
Haufe et al 2006. ³⁴	USA	Case series	Not reported	HSCs from pelvic bone marrow, 1 cc 1 cc of bone marrow aspirate (no modifications reported), followed by hyperbaric therapy	Yes	Single arm with 10 participants	Range 32–74	At 12M, there were no changes in reported VAS.

Abbreviations: abx, antibiotics; AE, adverse event; avg, average; BMAC, bone marrow aspirate concentrate; CFU, colony forming units; CLBP, chronic low back pain, FRI, functional rating index; HA, hyaluronic acid; HSC, hematopoietic precursor stem cells; IVD, intravertebral disc; M, month; MCID, minimal clinically important difference; MSC, mesenchymal stem cells; NDI, neck disability index; NPS, numeric pain score; NRS, numeric pain rating scale; ODI, Oswestry Disability Index; PL, platelet lysate, PLT, platelets; PSIS, posterior superior iliac spine; RCT, randomized controlled trial; SANE, modified single assessment numeric evaluation rating; SAE, serious adverse event.

health status assessed by the short-form-36 (SF-36) in three studies.^{20,31,35} One study used a modified single assessment numeric evaluation (SANE) rating scale between 0% and 100% with 0% indicating no improvement and 100% indicating complete pain relief.³² Eight studies used MRI^{20–24,28,29,31,32} with most assessing for Pfirrmann classification.

Study Funding

Three studies were sponsored by industry.^{20,23,32} Three studies were funded by institutional or government grants.^{21,22,24} Eleven studies did not report their funding source.^{25–31,33–35} However, the co-authors of two studies were employed by industry,^{33,35} and four studies received bone marrow concentrating devices from industry.^{26–30}

Risk of Bias and Quality Assessment

The Cochrane collaboration risk of bias tool was used to assess the three RCTs. (Figure 2).^{20–22} In the Noriega et al study, blinding of participants, clinicians, and outcome assessors along with incomplete outcome data, selective reporting, and other biases were graded as low risk for bias. There was a high risk of bias in random sequence generation based on the block randomization sequence. As for the follow-up study,²² there was insufficient information to determine the blinding of participants, clinicians, assessors, incomplete outcome data, and selective reporting.

In the Amirdelfan et al study, random sequence generation, incomplete outcome data, and selective reporting were graded as low risk for bias.²⁰ There was a high risk of bias with the lack of blinding of clinicians, associated research staff, and sponsors. Other risk of bias included a non-uniform diagnostic discography as a selection criterion.

The Newcastle-Ottawa scale was used to assess the 13 non-randomized observational studies (Table 2).^{23–32,34,35} The majority of the studies were given two stars for selecting participants with discogenic back pain and demonstrating that outcome of interest was not present at the start of the study.^{21–33,35} El Kadiry et al was the only study with control participants for comparison.²³ For outcomes, all studies followed their participants for at least one year.

GRADE Assessment of the Evidence

Based on the GRADE assessment, there is very low-quality evidence that BMAC and culture-expanded BM-MSCs are effective in reducing pain and disability and inducing positive anatomical changes. The GRADE assessment was completed by selecting “observation study” instead of “randomized trial” for the study design, even though there were three RCTs included in this review, to ensure a conservative assessment. The initial “low quality of evidence” was

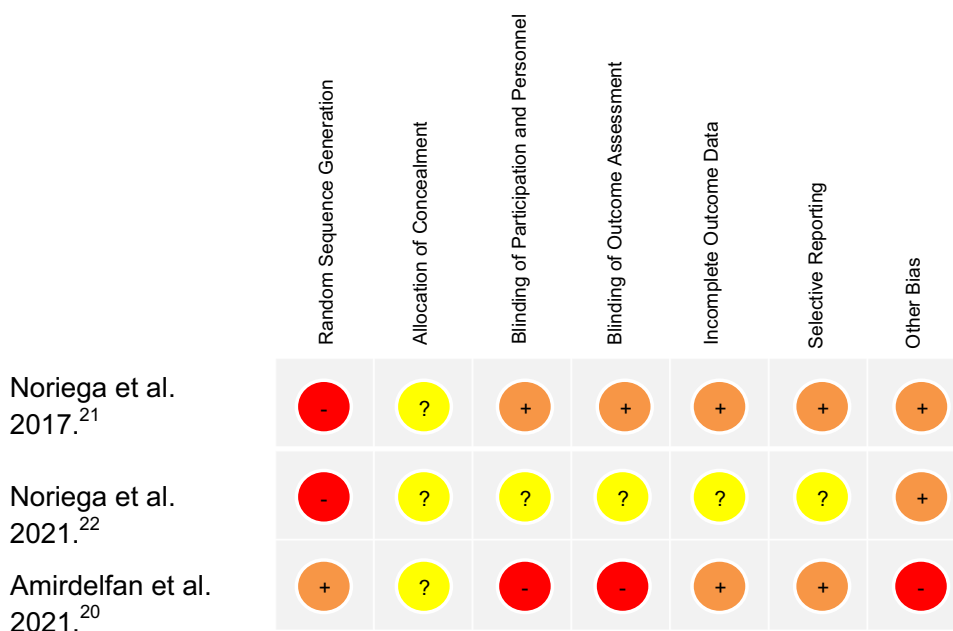


Figure 2 Risk of bias summary of randomized controlled trials based on authors’ judgements of each item.

Table 2 Bias Assessment for Observational Studies Using Newcastle-Ottawa Scale

Author	Year	Selection	Comparability	Exposure/Outcome
El-Kadiry et al ²³	2021	***	*	**
Orozco et al ²⁴	2011	**	-	**
Centeno et al ³²	2017	**	-	*
Pettine et al ²⁹	2015	**	-	**
Pettine et al ²⁸	2016	**	-	**
Pettine et al ³⁰	2017	**	-	**
Pettine et al ²⁶	2018	**	-	**
Pettine K.A. ²⁵	2017	**	-	**
Pettine et al ²⁷	2017	**	-	**
Elabd et al ³³	2016	*	-	*
Navani et al ³¹	2018	**	-	**
Wolff et al ³⁵	2020	**	-	*
Haufe et al ³⁴	2006	*	-	*

Notes: *Each *Indicates that the study satisfies a particular item on the Newcastle-Ottawa Scale. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of four stars can be given for the Selection domain, maximum of two stars can be given for the Comparability domain, and maximum of three stars can be given to the exposure/outcome domain. The more number of stars in each domain, the lower the risk of bias (eg ***Has less risk of bias than, **Which has less risk of bias than *).

downgraded to “very low quality of evidence” due to high risk of bias, inconsistency, indirectness, and imprecision. A summary of findings with quality of evidence for each outcome and reason for quality assignment is presented in Tables 3 and 4.

Primary Outcome: Pain Intensity Following Intradiscal Injection with BMAC or Culture-Expanded BM-MSCs

In general, studies highlighted that intradiscal injection with either autologous/allogeneic BMAC or culture-expanded BM-MSCs provided similar efficacy in participants with discogenic pain. All studies using an allogeneic source of BM-MSCs were culture expanded,^{20–22} and reported a significant improvement in pain scores and physical function after injection with culture-expanded BM-MSCs compared to controls. Studies using an autologous source were either BMAC^{23,25–31} or culture-expanded BM-MSCs.^{24,32,33} All studies that administered intradiscal injection with autologous BMAC or culture-expanded BM-MSCs similarly reported significantly improved pain intensity scores and physical function (ODI, BPI, SANE, SF-36) at the latest follow-up^{23–33} compared to baseline. Mean (or median) improvements in VAS/VPS (Verbal Pain Scale) pain scores at assessed time points were reported to be in 50–71% range in eight studies^{23,25–31} and below 50% in one study.²⁰ Improvements in functional and quality of life scores ranged from 10% to 90%.^{23,25–30,32,33,35}

One study that administered intradiscal injection with non-concentrated autologous bone marrow aspirate reported no improvement in pain or physical function at 12 months of follow-up compared to baseline.³⁴

Table 3 GRADE Summary of Findings Table

Patient or Population: Patients with Discogenic Pain Setting: Outpatient Intervention: Intradiscal Injection of BMAC/Culture-Expanded Bone Marrow MSCs Comparison: Controls or Baseline Pain			
Outcomes	№ of Participants (Studies)	Certainty of Evidence (GRADE)	Summary of Outcomes
Post-intervention pain score	144 (3 RCTs) ²⁰⁻²² 567 (13 observational studies) ²³⁻³⁵	⊕○○○ Very low ^{a,b,c,d}	Three RCTs and 13/14 observational studies reported significant improvement in VAS/NPS pain score at follow-up of ≥12 months compared to controls or baseline pain. 1/14 observational study showed no improvement in VAS pain score.
Post-intervention functional score	144 (3 RCTs) ²⁰⁻²² 567 (13 observational studies) ²³⁻³⁵	⊕○○○ Very low ^{a,b,c,d}	Three RCTs and 13/14 observational studies reported significant improvement in functional score (ODI, BPI, SANE, SF-36) at follow-up of ≥12 months compared to controls or baseline function.
Post-intervention Pfirrmann grading	144 (3 RCTs) ²⁰⁻²² 567 (13 observational studies) ²³⁻³⁵	⊕○○○ Very low ^{a,b,c,f}	One RCT reported no significant radiographic improvements. Two RCT reported improved Pfirrmann grading compared to controls. 5/14 observational studies reported improved Pfirrmann grade in some of the patients post-intervention.

Notes: GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. a. One RCT used block randomization sequence. Two RCTs did not blind the clinicians, associated research staff, and sponsors. Refer to risk of bias summary table Most observational studies introduced a high risk of bias in “selection”, “comparability of cohorts”, and “assessment of outcome.” Refer to quality rating table b. High heterogeneity was present in the studies. c. Some studies performed multiple intradiscal injections, some studies performed intradiscal injection and epidural injection, and some studies performed intradiscal injection and posterior chain injections. d. Success rates were associated with wide ranging and overlapping confidence intervals. f. Changes in Pfirrmann grade were not statistically significant in all groups.

Table 4 Certainty of Evidence Assessment

Certainty Assessment						
№ of Studies	Study Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other Considerations
Post-intervention pain score						
16	3 RCTs ²⁰⁻²² 14 observational studies ²³⁻³⁵	Serious ^a	Serious ^b	Serious ^c	Serious ^d	None
Post-intervention functional score						
16	3 RCTs ²⁰⁻²² 13 observational studies ²³⁻³⁵	Serious ^a	Serious ^b	Serious ^c	Serious ^d	None
Post-intervention Pfirrmann grading						
16	3 RCTs ²⁰⁻²² 13 observational studies ²³⁻³⁵	Serious ^a	Serious ^{b,f}	Serious ^c	Serious ^{d,f}	None

Notes: ^aOne RCT used block randomization sequence. Two RCTs did not blind the clinicians, associated research staff, and sponsors. Refer to risk of bias summary table Most observational studies introduced a high risk of bias in “selection”, “comparability of cohorts”, and “assessment o outcome.” Refer to quality rating table ^bHigh heterogeneity was present in the studies. ^cSome studies performed multiple intradiscal injections, some studies performed intradiscal injection and epidural injection, and some studies performed intradiscal injection and posterior chain injections. ^dSuccess rates were associated with wide ranging and overlapping confidence intervals. ^fChanges in Pfirrmann grade were not statistically significant in all groups.

Secondary Outcome: Relationship Between Number of Cells Injected and Reported Outcomes

One study found a positive trend with higher number of injected cells and better improvement in pain and physical function. Pettine et al reported that participants' BMAC with ability to form more than 2000 Colony-forming unit fibroblasts (CFU-F)/mL, regardless of age, had significant VAS and ODI improvement compared to participants receiving BMAC with less than 2000 CFU-F/mL.^{26,28–30} Elabd et al showed a linear relationship between the total number of culture-expanded BM-MSCs injected and improvement in the overall quality of life.³³ Amirdelfan et al reported a significant difference between the four treatment groups (participants receiving 18 million BM-MSCs, 6 million BM-MSCs, Hyaluronic Acid and Saline Control) and time to treatment failure. Additionally, only the cohort receiving 18 million BM-MSCs showed a greater improvement from baseline in the physical component score (SF-36) compared to control participants at 36 months.²⁰

Characterization of BMAC or BM-MSC products was performed in some included studies. Typically, MSCs are characterized by: (1) adherence to plastic under standard culture conditions, (2) expression of CD105, CD73 and CD90, (3) lack expression of CD45, CD34, CD14 or CD11b, CD79 α or CD19 and HLA-DR and (4) ability to differentiate to osteoblasts, adipocytes and chondroblasts.^{37–40} Centeno et al and Elabd et al did not report cell characteristics but described cell harvesting and specified culturing of the cells in a hypoxic environment.³³ El Kadiry et al²³ reported that BMAC was enriched with mononuclear fraction containing MSCs (CD45–CD44 + CD90+CD105+). Several studies by Pettine et al^{28–30} reported average BMAC contents of TNC/mL and CFU-F/mL and tested cells for superficial markers such as MSC-specific CD90+, CD105+ and endothelial type CD34+. Amirdelfan et al²⁰ reported using allogeneic stromal precursor antigen-3 (STRO-3) immunoselected MPCs. Noriega et al,^{21,22} Orozco et al²⁴ and Wolff et al³⁵ did not specify cell characteristics.

Secondary Outcome: Anatomic Changes Based on MRI Assessment

Included studies used MRI^{20–24,29,32} to assess for structural changes after intradiscal injection with BMAC or culture-expanded BM-MSCs. El-Kadiry et al reported increased disc height and spinal canal space size without worsening disc quality on MRI scans in participants at 8 and 12 months after intradiscal injection.²³ Noriega et al demonstrated that Pfirrmann grading favors the culture-expanded BM-MSC-injected group, and this favorable grading was maintained up to 42 months while there were no statistically significant changes (defined by p-value > 0.05) in disc heights and water content between the cohort that received culture-expanded BM-MSCs versus controls.^{21,22} Orozco et al reported significant elevated water content in the disc even though the disc height did not change.²⁴ Centeno et al and Pettine et al reported regression of posterior disc bulge following intradiscal treatment.^{29,32} Amirdelfan et al reported no significant modified Pfirrmann score changes in any of the groups post-injection at all follow-up evaluations.²⁰

Discussion

Synthesis of current evidence without pooling revealed that: (1) intradiscal injection with autologous or allogeneic BMAC/culture-expanded BM-MSCs generally provided improved pain intensity and physical functioning in participants with discogenic pain compared to their baseline scores and/or control groups and (2) intradiscal injection with BMAC or culture-expanded BM-MSCs may lead to MRI evidence of improved disc height, disc water content, or improved Pfirrmann grading although these imaging findings were not consistent across all included studies. Intradiscal injection with BMAC/culture-expanded BM-MSCs in participants with discogenic pain was associated with significant improvement in pain intensity and physical function post-injection between one to six years in the included studies. Participants with lumbar intradiscal injection experienced improved pain and function with significantly decreased opioid use.^{23,31} More than 70% of the participants did not undergo spine surgery throughout follow-up for six years.^{25,26,28–30} Similarly, participants with cervical intradiscal injection reported improved pain and function at 24 months of follow-up.²⁵ However, the overall level of certainty for the potential associations made in this systematic review is low, because there is very low-quality GRADE evidence to support these.

The analgesic benefits from BMAC and BM-MSCs are likely related to their immunomodulatory profile once injected into the disc. For example, BMAC contains MSCs, platelets, white blood cells, cytokines and growth factors, including Platelet-derived Growth Factor (PDGF), Transforming Growth Factor Beta (TGF- β), and Bone Morphogenetic Protein (BMP)-2 and BMP-7.^{41,42} BMAC also has clinically relevant concentrations of Interleukin-1 receptor antagonist (IL-1Ra), a natural inhibitor of the pro-inflammatory effects of interleukin 1.⁴³ The potential to reduce pain, decelerate IDD, or restore the IVD is less likely related to the MSC's capability of self-renewal and differentiation. Instead, it is likely related to MSC ability to secrete trophic and immunomodulatory factors.⁴⁴⁻⁴⁶ While future larger scale RCTs are warranted to confirm this association of positive analgesic and physical functioning benefits, the current evidence suggests very-low quality evidence that intradiscal injection of BMAC and culture-expanded BM-MSCs may improve discogenic pain. Thus, this modality may be offered to patients who fail first-line treatment (physical therapy, epidural steroid injection) and before pursuing more invasive spine surgery.

Additionally, intradiscal injection of other biologic agents have also been studied. Intradiscal injection of PRP for discogenic pain has been assessed in two systematic reviews, which reported a total of five observational studies consisting of 90 participants treated with 1–2mL of PRP.^{47,48} These reviews evaluating intradiscal injection of PRP for discogenic pain reported an overall reduction in pain scores, reduction in ODI scores at 6 months and improvement in functional score in one RCT which persisted for one year.⁴⁷⁻⁴⁹ There are a limited number of studies that used non-BM-MSCs for intradiscal disease. Three published case series⁵⁰⁻⁵² with a total of 27 participants used autologous adipose-derived MSCs, stromal vascular fraction (SVF), and allogeneic umbilical cord-derived MSCs. They reported improved pain at 6 months and improved functional outcomes. Although the focus of our systematic review was on BMAC and BM-MSCs, future studies should query whether other injectable biologic treatments may offer similar benefits to BMAC and culture-expanded BM-MSCs.

Interestingly, studies assessing participants who received BMAC and culture-expanded BM-MSCs had longer follow-up periods and sustained pain relief up to 72 months while other studies assessing PRP and other sources of MSCs reported follow-up periods of only 6–12 months.

In our systematic review, there was a small subset of participants that experienced decreased efficacy after intra-discal injection of BMAC or culture-expanded BM-MSCs. For these participants, potential factors that may contribute to the lack of response include inadequate number of cells injected,^{20,29} inadequate quality of cells injected,³⁴ participant's age,²⁹ other confounding spine disorders²⁷ or comorbidities, and the severity of the degenerated IVD prior to injection. These factors have been referenced as negative predictive factors in other musculoskeletal disorders treated with MSCs. Mao et al reported that the optimal quantity of stromal cells may be a 10^8 magnitude to stop or slow disease progression and degeneration.⁵³ Amirdelfan et al suggested that at least 18 million of immunoselected MSCs were required for physical improvement compared to controls in treating discogenic back pain.²⁰ In Haufe et al, participants received non-concentrated bone marrow aspirate, which would be considered a poor quality injectate, and experienced no change in pain relief or functional improvement.³⁴ Furthermore, age can negatively impact the ability of MSCs to rejuvenate and regenerate. In *in vitro* studies, age-related epigenetic modifications decreased the regenerative potential of MSCs.^{54,55} In animal studies, increasing donor age impaired bone marrow cell therapy efficacy regardless of disease severity in the recipient.⁵⁶

Safety

In our review, adverse events included injection related-pain and a case of discitis. Amirdelfan et al reported greater adverse events in the 18 million MPC-treated group compared to the 6 million MPC-treated group, HA group, and normal saline groups. One participant in the 6 million MPC-treated group developed discitis. The overall safety is consistent with reports in the literature regarding MSC injection for various musculoskeletal complaints.⁵⁷ There have only been rare previous reports of adverse events such as development of hyperplastic gliosis that caused cauda equina syndrome.^{58,59} However, culture-expanded BM-MSC production requires sophisticated laboratory equipment with experienced staff in current Good Manufacturing Practice facilities to eliminate risks associated with cell manipulation. Hence, development of homogenous “standardized” cell lines such as allogeneic or *eg* immunoselected allogeneic cells in study by Amirdelfan et al may potentially be safer, more cost effective, and available “off the shelf”. It could also reduce donor dependent variation in ability to produce anti-inflammatory substances.

BMAC may possess seemingly less product heterogeneity, but use of different concentration devices may yield distinct products with distinct regenerative and immunomodulatory profiles.⁶⁰ In our systematic review, studies have not always reported which devices were used, and therefore we could not compare the safety and efficacy among different production strategies. In addition, bone marrow aspiration technique may also potentially introduce more variability in MSC contents and details of the aspiration technique were not provided.⁶¹

Allogeneic vs Autologous BMAC and Culture-Expanded BM-MSCs

Advantages of using autologous BMAC include ease of sample processing since aspiration and injection can be performed in two subsequent procedures on the same day. The risk of graft versus host disease and infection transmission from one person to another is eliminated with autologous products, however, there is always a chance of sample contamination. Autologous BMAC may not undergo as vigorous testing as mass-produced culture-expanded MSCs therefore there is potentially a higher risk of MSC product alteration. Some drawbacks to clinical use of autologous BMAC include the high cost of processing single batches at a time, variability of sample quality and, if culture-expanded MSCs are used, increased time to allow for meaningful doses.⁶² The treatment with BMAC falls under minimally manipulated product, and therefore, does not require Food and Drug Administration (FDA) approval. If MSCs are isolated from bone marrow aspirate, stored, and expanded, then it is no longer considered a minimally manipulated product and requires an extensive FDA approval process. There are risks associated with the above-described processing such as contamination of cultures or creation of otherwise altered cell lines; but this further processing allows for applications of allogeneic “off the shelf” products, which is similar to the product that was used in the study by Amirdelfan et al. Allogeneic MSC sourcing would also allow for large-scale batch production, facilitate improvement and confirmation of product quality, consistency and safety profile, and allow for easier product availability. Important considerations for treatment efficacy remain as they relate to donor age⁶³ and donor comorbidities,⁶⁴ and therefore inter-donor MSC variability may impact the quality of cell products.

Cell Dose and Outcomes

One study suggested that higher cell dosing may improve analgesic outcomes²⁹ and two other studies noted some milder improvements in quality of life and SF-36 score with higher doses.^{20,33} The number of any type of cells injected in one disc ranged markedly from 1.7 million to as much as nearly 390 million cells. Proceduralists may consider increasing cell number in the injectate to optimize therapeutic response. However, future studies are warranted to validate this association and determine if the association is truly dose-dependent versus dose-independent with requirement to meet a minimum threshold of cell number. Furthermore, injected volume and type of medium may also be important given the small anatomical space in the disc ranges on average between 1 and 3 mL.⁶⁵ This volume may easily approach the typical volume of contrast and saline injected during discography for lumbar discs, however one study also injected up to 6 mL without adverse events.

Imaging Selection

Several studies identified favorable anatomic changes based on MRI and Pfirrmann scores after injection with BMAC or culture-expanded BM-MSCs. In clinical practice, MRI has been the most sensitive imaging method to identify changes in degenerated discs. Suggestion for future studies may include use of more detailed radiological scoring such as Modic changes which frequently correlate with discogenic low back pain, high-intensity zones, and other anatomical changes.⁶⁶ Spinal X-rays have limited utility given that they can only show decreased disc space, vacuum phenomena and osteophytes and may not capture subtle structural changes.

Provocative Discography

Discography was performed in the majority of studies (10 of 16 studies) but not always for all participants. In clinical practice and patient population with chronic back pain, provocative discography has been an infrequently used method for chronic back pain resistant to treatment, to help decide if there is any indication for surgery, and to determine whether the suspected disc is the true pain generator. Commonly, other diagnostic studies are performed before approaching discograms. While an MRI can be helpful in assessing disc degeneration by looking at Pfirrmann score, Modic changes, and high

intensity zones, discography with its mechanical effects can help diagnose if the IVD is the pain generator. Another potential benefit is that it can identify an annular tear and ability to contain biologic injectate within the disc.⁶⁷ While we are unable to determine whether discogram contributed to participants' positive outcomes and ability to select participants with true discogenic pain, we hypothesize that it may be a beneficial diagnostic tool to help determine source of pain and demonstrate an intact annulus that can contain and accommodate biologic injectate. However, disadvantages of using provocative discography include procedural disruption of the annulus fibrosus and potential worsening degeneration of the disc associated with disc herniation. This risk was demonstrated in a matched-control prospective study despite the use of 22–25 Gauge needles.⁶⁸ Therefore, it might be helpful to consider discography with a consistent protocol in future studies as an inclusion criteria alongside other imaging modalities while keeping in mind its potential risks.

Limitations

Several limitations are notable. There was a high risk of bias, small sample sizes, and lack of comparator arms in many included studies. This is consistent with prior narrative reviews on injectable biologics for the treatment of intradiscal disease.^{69–71} Variation both between and within studies was present in design for participants' selection, cell preparations (volume type and concentration of cells in injectate), levels of disc injection (cervical versus lumbar spine), and follow-up. For example, out of the 10 prospective studies, only one used provocative discography to confirm discogenic pain as an inclusion criterion.²⁴ In the RCT studies, provocative discography was either left to the investigator's discretion²⁰ or not performed at all.^{21,32} There are concerns about the lack of blinding of the participants, clinicians, and research staff.²⁰ Lastly, industry funding and influence may add additional bias to the current evidence.^{20,23,32} In addition, this study is limited by very low-quality GRADE evidence.

Future Directions

Several strategies for future studies should be considered. First, most studies did not report characteristics such as cell surface markers for their BMAC products, though some used a set of MSC-specific markers (eg CD 90, 105, CD166, CD44) to demonstrate that there is a population of MSCs. We encourage future studies to report MSC-specific, hematopoietic, and endothelial cell surface markers. Protein analysis to document contents of anti-inflammatory molecules and cytokines in the BMAC product would also be beneficial to assess capacity to treat discogenic pain. In addition, there are important questions to be raised in future studies to ensure optimal clinical results such as selection of appropriate participants and discs that will benefit from MSCs or BMAC, using clinical symptoms, specific imaging findings (eg Pfirrmann scores) or discography while considering participants' age and comorbidities. Second, MSC and BMAC have been mostly studied *in vitro* under ideal external conditions. There remain many questions regarding MSC survival and efficacy *in vivo* given the relative unavailability of nutrients and oxygen in the IVD environment that may be detrimental.⁷² Henriksson et al⁷³ reported in their study of four participants that MSCs may be able to survive and proliferate in the IVDs for 6–12 months post-injection but they were undetectable at 28 months. Therefore, further studies assessing the long-term survival of MSCs for at least 12 months should be conducted as restoration of the IVD microenvironment and proteins are unlikely to occur within a shorter period of time.⁷² To detect improvements, more objective markers such as radiographic evidence from MRI are needed to quantify anatomical changes in the disc after treatment with injectable biologics. Though we are hopeful that MSC/BMAC remain contained within the IVD after injection, in cases when the annulus fibrosus is disrupted, it is possible that MSC leakage occurs. Use of provocative discography suggested better accuracy in determining painful discs and proof of cell containment however, there are risks associated with the procedure that need to be considered.

These data would inform the critical quality attributes needed in the creation of a reproducible, cost-effective and commercially available product. The availability of an approved injectable “off-the-shelf” MSC product would allow for easier incorporation into the real-world clinical practice. To facilitate the efficacy of such a product, the optimal delivery method, including the possibility of using delivery vehicles like hydrogels, needs to be identified to prevent MSC leakage.⁷⁴ The long-term safety in cases of human leukocyte antigens (HLA) mismatch should also be established.⁷⁵

In this review we focused on BMAC and MSCs, however other cell products such as nucleus pulposus (NP) and chondrogenic cells or PRP were also commonly investigated as potential biologics for IVD^{76–80} and comparison with MSC and BMAC would be of interest.

Finally, future high-powered RCTs utilizing homogeneous selection criteria may help inform future systematic reviews where outcomes may be pooled.

Conclusion

This study overall supported modest efficacy in treating discogenic pain and improving functional outcomes with BMAC or MSC injections, however, the level of certainty for the potential associations made in this review is low as documented by very low-quality GRADE evidence to support these conclusions. Generally, improvements in pain and functional scores compared to baseline were found in most studies using either BMAC or BM-MSCs and there were some mild objective improvements noted on spinal MRIs in some studies. Major limitations included significant heterogeneity among participants, limiting generalizability such as areas of pain and variability in types and quantities of treatments, small sample sizes with small or no control groups, high risk of bias, inconsistency in determining painful discs, lack of blinding, and industry funded studies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare.

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